# Guidelines for Improving Outcomes in Gynaecological Cancers

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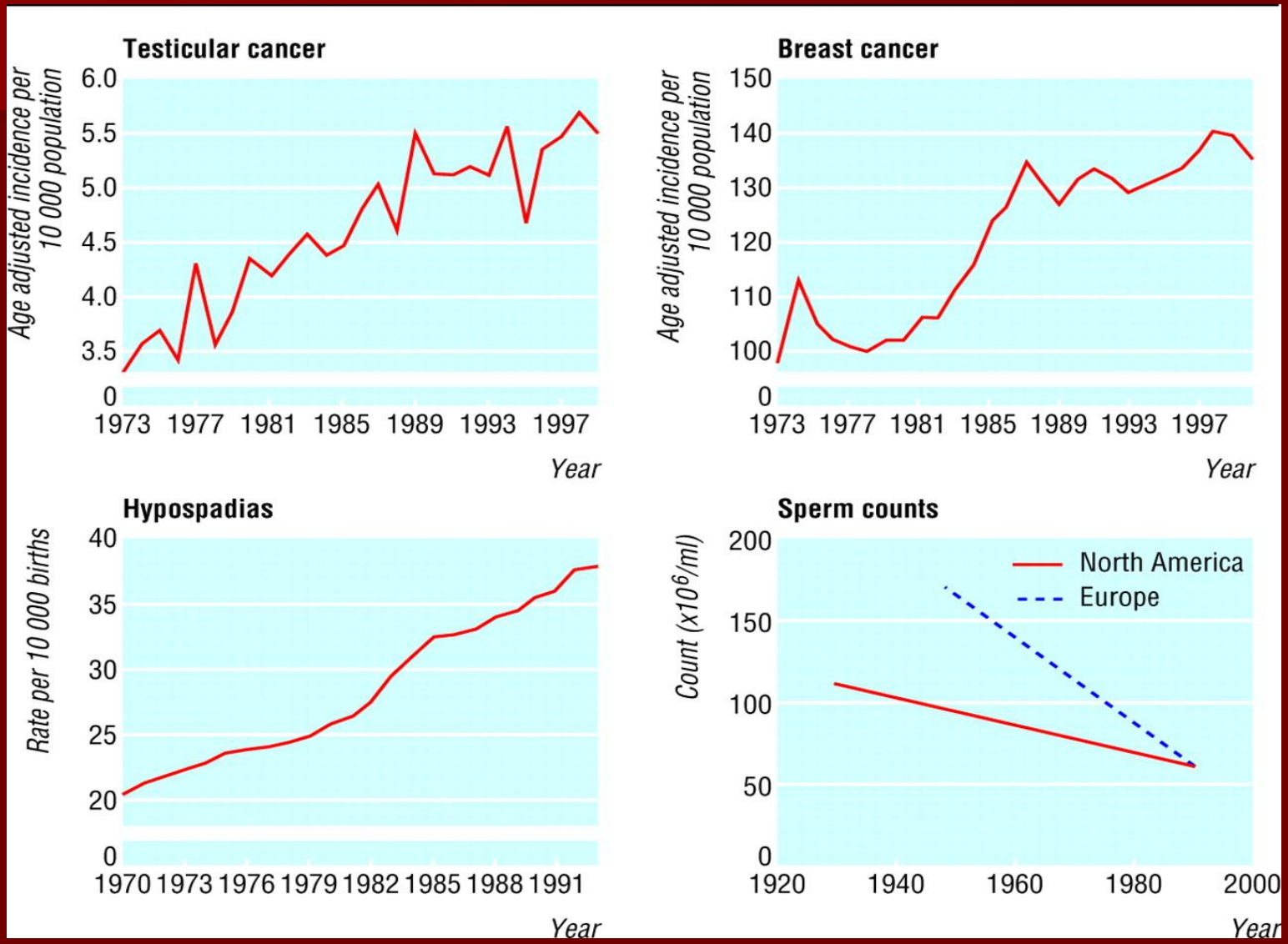
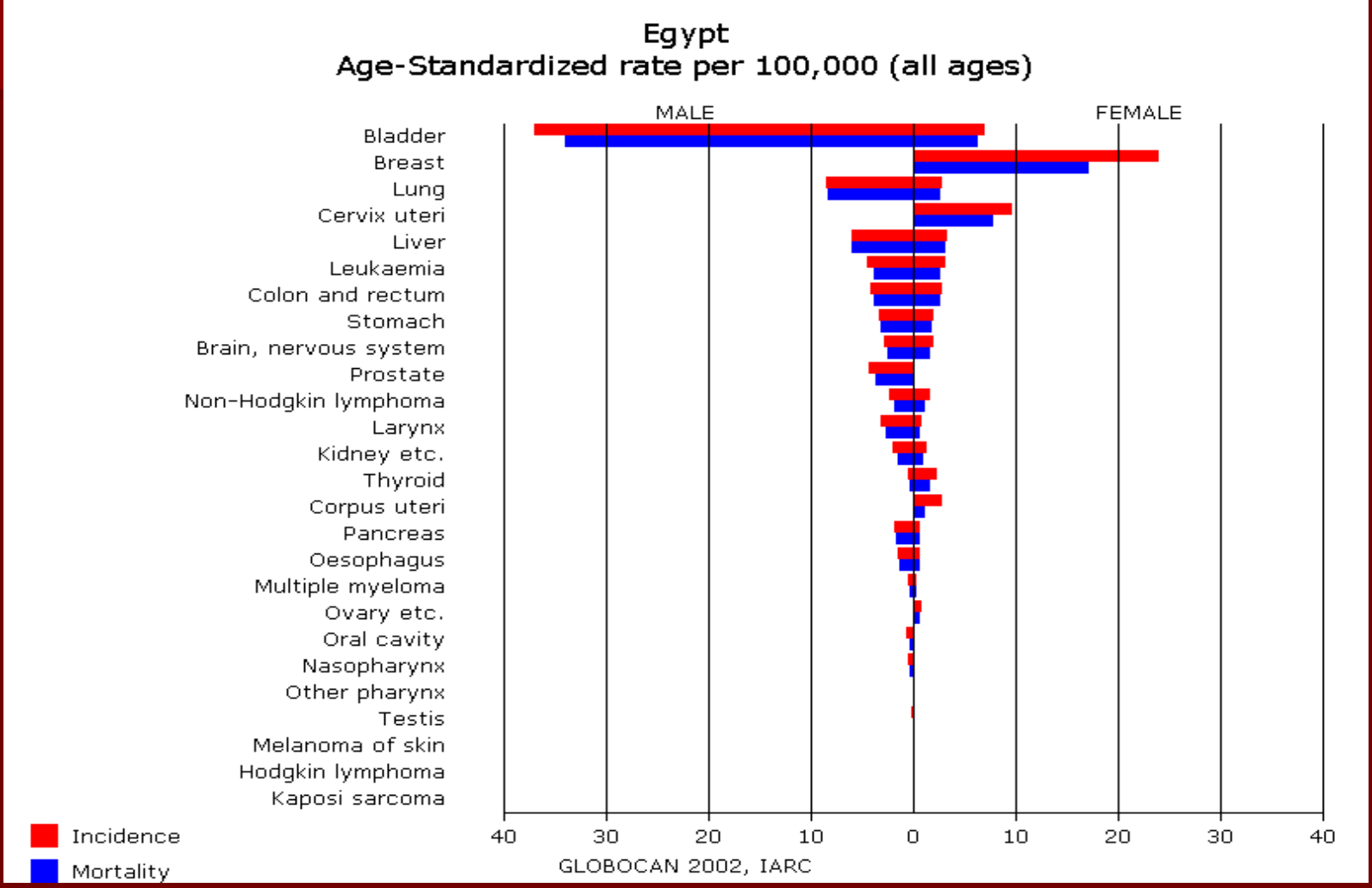
# Global Female Cancer : Incidence & Mortality (2002)

| | Incidence | | | Mortality | | |
|---|---|---|---|---|---|---|
| | | Crude rate | ASR | | Crude Mortality Rate | ASR |
| Breast | **1151298** | 37.4 | 37.4 | **410712** | 13.3 | 13.2 |
| Cervix | **493243** | 16 | 16.2 | **273505** | 8.9 | 9 |
| Colorectal | **472687** | 15.4 | 14.6 | **250532** | 8.1 | 7.6 |
| Lung | **386891** | 12.6 | 12.1 | **330786** | 10.7 | 10.3 |
| Stomach | **330518** | 10.7 | 10.4 | **254297** | 8.3 | 7.9 |
| Ovary | **204499** | 6.6 | 6.6 | **124860** | 4.1 | 4 |
| Corpus uteri | **198783** | 6.5 | 6.5 | **50327** | 1.6 | 1.6 |

# Trends in reproductive health



# Cancer in Egypt



# Early Cancer Detection Unit
# Ain Shams University
# 1992-2006

| | |
|---|---|
| Endometrial cancer | **521** + 34 metastatic |
| Cervical cancer | **517** + 111 metastatic |
| Ovarian cancer | **323** epithelial<br>**68** non epithelial |
| Vulval cancer | **98** |

# Management of genital malignancy often leads to

- Loss of fertility
- Disfigurement and mutilation
- Crippling treatment complications
- Changes in life and family plans

# Expectations

- More young women are expected to have cancer
- More women are expected to have their first pregnancy at an older age
- Some women will develop cancer during pregnancy

# Expectations

- Women are expected to live longer
- Women expect better results of therapy *(no failure)*

# Why specialist referral

- Patients
  - Better survival and quality of life
  - Continuity of care with no delays or gaps
- Physicians & Nursing staff
  - Concentration of cases
  - Build of expertise
  - Better training
- Research: better conclusion of trials
- Cost effectiveness implications

# Why specialist referral

- No place for surgical adventures
- No place for “one man show”
- Inappropriate primary interventions may make appropriate treatment plans difficult to achieve even after specialist referrals

# Gynaecological cancer management

- Preoperative diagnosis and patient assessment
- Plan of treatment (multimodal) (tailor-made)
- Life time follow up plan
- Rehabilitation and palliative care
- Social and familial support

# Gynaecological Cancer Management:

## Multi-Disciplinary Team (MDT)

- Gynaecological oncologist √
- Radiotherapist √
- Clinical oncologist !
- Radiologist √
- Histopathologist √
- Clinical nurse specialist √
- Palliative care and pain management specialist !

# Gynaecological Cancer Management:

## **Multi-Disciplinary Team (MDT)**

MDT operate in harmony as an orchestra not as solo players

# Specialist gynaecological cancer management:

## The obstacles

- Physicians: economic incentive, surgical impulse, individuality
- Economics
- Organisational (national and hospital)
- Patients: misinformation, non compliance, socioeconomics

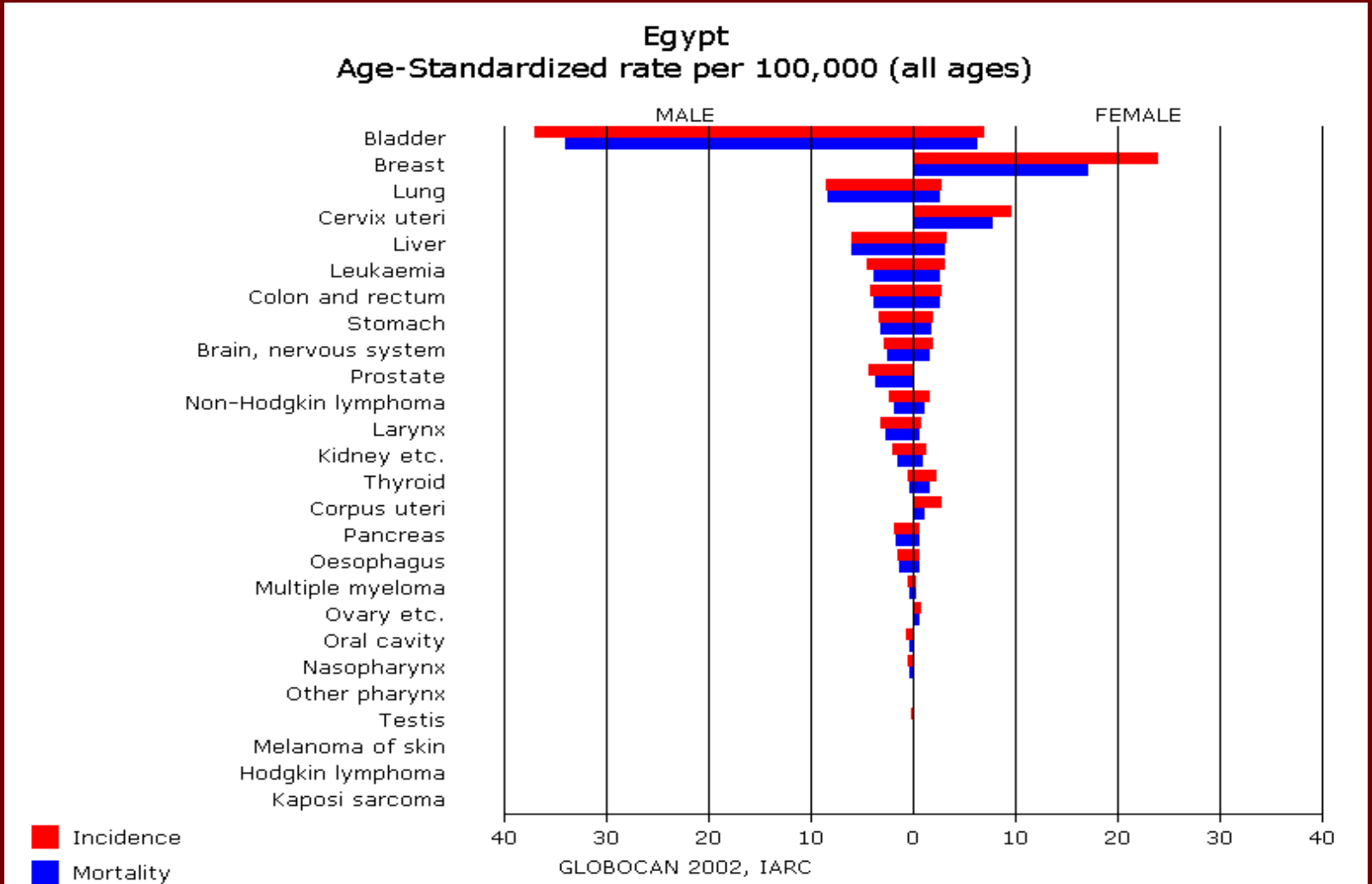
# Referral to Specialist Gynaecological Oncology

- Women with endometrial cancer other than endometrioid type grade I/II stage IA/IB
- Women with ovarian cancer and suspicious ovarian masses
- Women with cervical cancer whatever the stage
- Women with vulval cancer
- Women with vaginal cancer

# Guidelines for the management of

Endometrial cancer

# Endometrial Cancer in Egypt
# 730 / Year (2.9/100,000)
# 298 Mortality (0.9/100,00)



# Risk Factors

- Approximately 50 percent of endometrial carcinomas occur in women with particular risk factors for the disease.

- Excessive estrogen is associated with most of the risk factors that have been linked to endometrial carcinoma

# Endometrial Cancer: Risk factors

- Unopposed estrogen
- Obesity
- Nulliparity
- Early menarche
- Late menopause
- Chronic anovulation
- Family history of breast, ovarian or colon cancer
- Past history of breast or colon cancer
- Hepatic failure
- Granulosa cell tumors
- Polycystic ovary syndrome
- Diabetes mellitus

# Endometrial Cancer: Risk factors

| | Relative risk |
|---|---|
| Overweight† | |
| – 9–23 kg (20–50 lb) | 3.0 |
| – 23 kg (50 lb) | 10.0 |
| No children (vs. 1 child) | 2.0 |
| No children (vs. 5 children) | 5.0 |
| Late menopause (age, 52 yr or later vs.49 yr) | 2.4 |
| Diabetes mellitus | 2.7 |
| Unopposed estrogen therapy | 6.0 |
| Tamoxifen therapy | 2.2 |
| Use of sequential OCPs | 7.0 |
| Use of combined OCPs | 0.5 |

*Dubeau et al. 1993*

# Endometrial cancer: Diagnosis

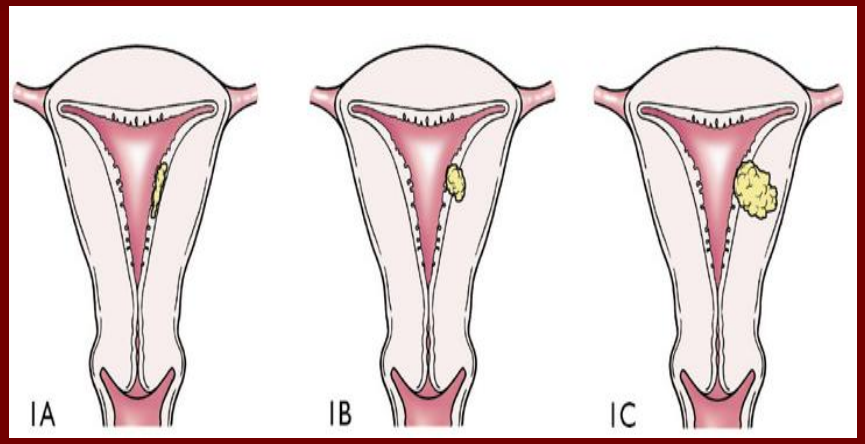
Objectives

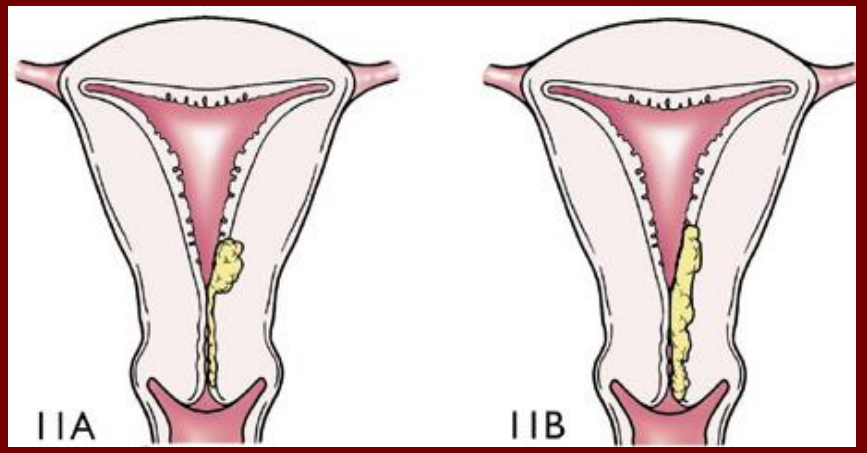
- Diagnosis of endometrial cancer
- Identification of prognostic factors
- Preoperative provisional staging
- Plan for treatment including referral to specialised centers

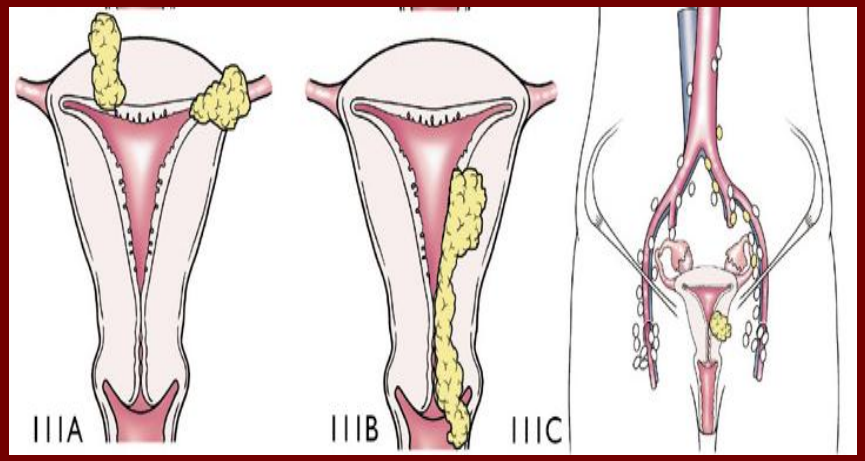
# Endometrial cancer: Prognostic factors

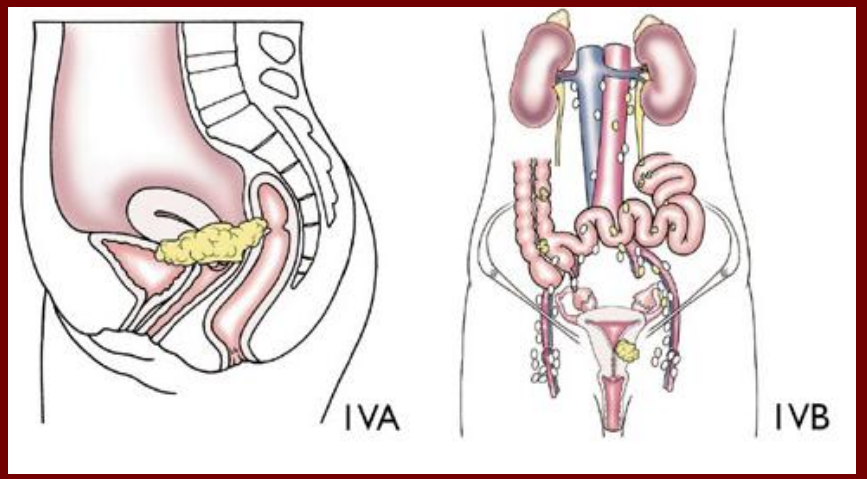
- Depth of myometrial invasion
- Positive peritoneal washings
- Histologic grade
- Histologic type (CCC, UPS, MMM)
- DNA ploidy
- Lymphatic vascular space invasion
- Tumour size
- Estrogen & progesterone receptors
- Patient's age

# Endometrial cancer: Staging



# Endometrial cancer: Diagnosis

- Diagnostic techniques *(Combined)*

  -Endometrial sampling

  -Transvaginal ultrasonography (endomet. >5mm)

  *(69-86% sensitivity for detecting myometrial invasion)*

  -Hysteroscopy

  -Dilatation & curettage *(if sampling fails)*

  -MRI

# Endometrial cancer: Diagnosis

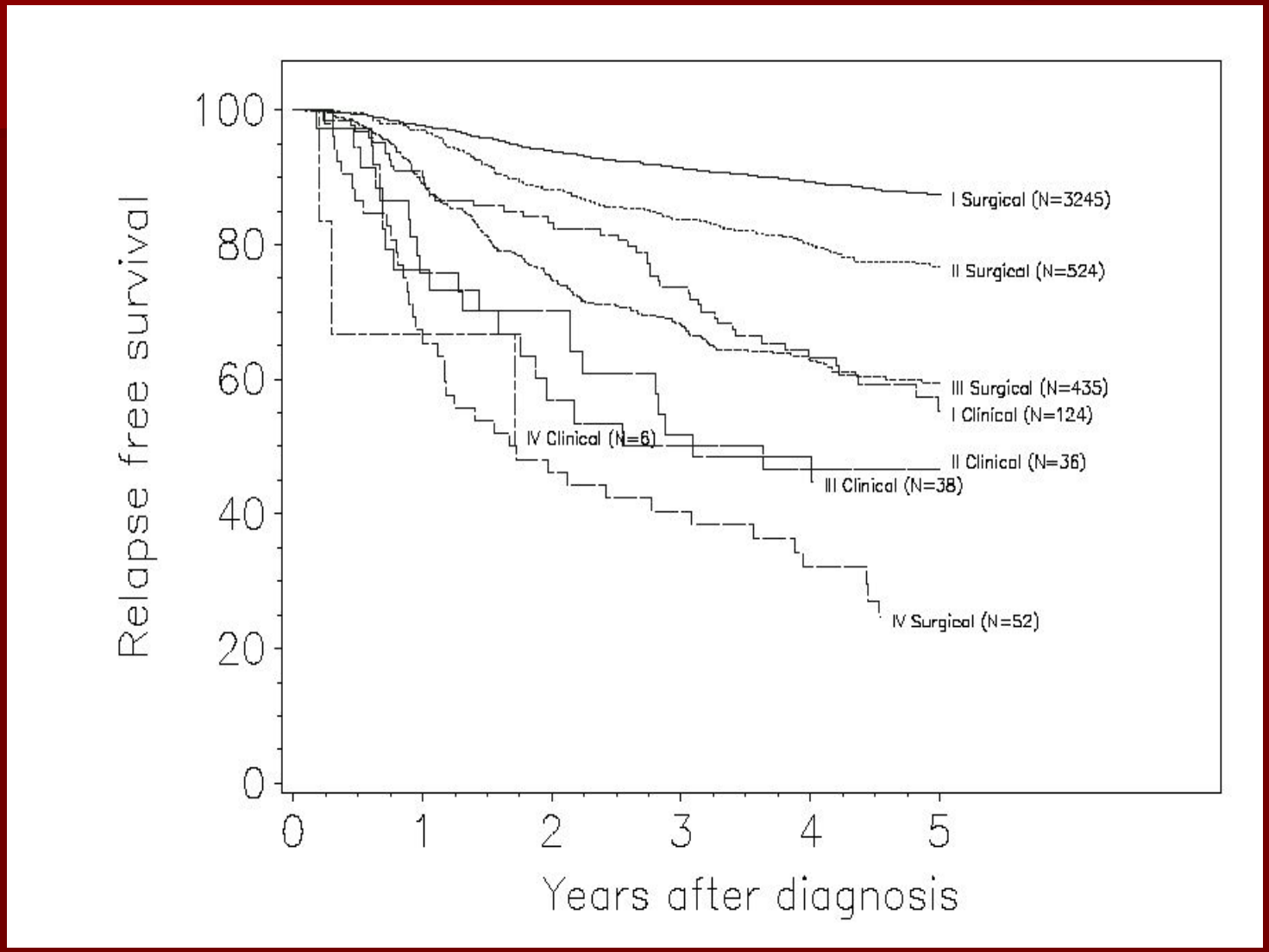
MRI preoperative staging

- Detects myometrial invasion with sensitivity 75-88% *Sironi et al. 1992, Kinkel et al. 1999*
- Whichever method 10-15% will be under staged
- It is a good practice to refer stages higher than Ib to specialised centers

# Endometrial cancer: Staging

- **Clinical staging**: Old, not adopted by FIGO
- **Surgical staging**:
  - Peritoneal washing for cytology
  - Total hysterectomy with bilateral salpingo-oophorectomy (radical hysterectomy ?)
  - Pelvic lymph node sampling
  - +/- Para-aortic lymph node sampling
  - Omentectomy in clear cell, UPS or metastases

# Endometrial cancer: Survival by Mode of Staging



# Endometrial cancer: Adjuvant therapy

- Radiotherapy
- Chemotherapy
- Hormonal therapy *(of no value for early but may be used in recurrent or metastatic disease*

# Endometrial cancer:
# Adjuvant radiotherapy in stage I

- Survival benefit in stage IC grade 3,4

*Lee et al. JAMA, Jan. 2006*

- IA, IB grade I,2 have lower loco-regional recurrence but no survival benefit

*PORTEC study; Creutzberg et al.2000,*
*Scholten et al.Nov.2005*

# Endometrial cancer: Adjuvant therapy in stage III & IV

Including high risk types UPS, CCC, MMM

- Chemotherapy of adriamycine and platinum offers survival advantage over whole abdomen radioth.

*Randall et al. 2006 GOG trial*

- Taxol adds little benefit

# Endometrial cancer: Follow up

- Follow up is clinical
- No value for routine imaging
- No value for vaginal vault cytology

# Guidelines for the management of

Ovarian cancer

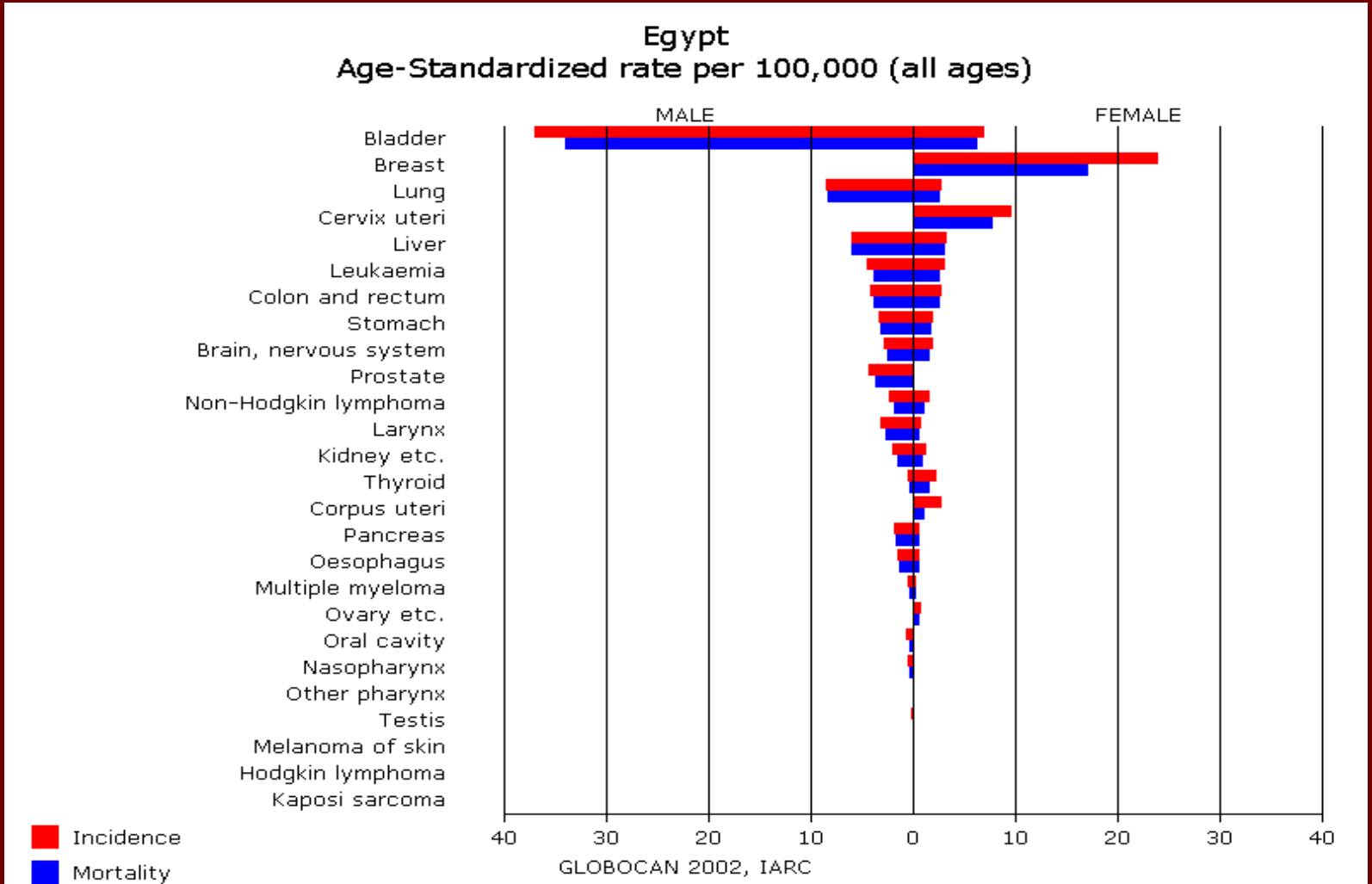
# Ovarian Cancer

- Life time risk: 1 in 70
- Incidence: 3.3 - 25.3 in 100,000
- Incidence is rising 1% every year in western world
- Incidence and mortality increases with age (>65 years)
- Leading cause of death from genital malignancy

# Ovarian cancer

- 90% are epithelial
- 75% are discovered late (stage III-IV)
- 5-year survival depends on stage (90% for stage I and 3-5% for stage IV)
- 1-10% are hereditary

# Ovarian Cancer in Egypt
# 276 / Year (0.8 /100,000)
# 194 Mortality (0.6 /100,00)



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# Ovarian cancer

## Ain Shams University Hospital
## Gnaecological Oncology Unit
## (1995 - 2000)

| | | |
|---|---|---|
| **Endometrial cancer** | **273 cases** | |
| **Ovarian cancer** | **270 cases** | **(195 primary)** |
| **Cervical cancer** | **161 cases** | |
| **Vaginal cancer** | **52 cases** | |
| **Vulvar cancer** | **51 cases** | |

# Ovarian cancer

- 90% are epithelial
- 75% are discovered late (stage III-IV)
- 5-year survival depends on stage (90% for stage I and 3-5% for stage IV)
- 1-10% are hereditary

# Risk for Ovarian Cancer

Increased by

- Nulliparity
- Early menarche and late meopause
- Infertility and infertility medications
- Family history
- Ainmal fat, milk and high protein & calorie intake.

Decreased by

- Parity *( 30-60% reduction)*
- OCP *(25-80% reduction)*
- Lactation *(40% reduction)*
- Tubal ligation *(15-87%)* and hysterectomy *(12-34%)*

# Ovarian Cancer Pathogenesis

???????

Incessant ovulation (Fathalla)

Hypergonadotrophins

Pelvic contamination

Genetic

Multifactorial

# Ovarian cancer: Prognostic factors

**Stage•**

Age•

**Residual disease•**

Ascites•

Tumour grade•

DNA aneuploidy *(Borderline and early stage tumours)*•

Oncogene products: HER-2/neu, p21•

Tumor suppressor gene: p53. pRB•

Drug resistance markers: GST, Pgp •

# Ovarian cancer: Prognostic factors

- Stage
- Age
- Residual disease
- Ascites
- Tumour grade
- DNA aneuploidy *(Borderline and early stage tumours)*

# Ovarian cancer prevention

- Early pregnancy, breast feeding, OCP for birth control
- Avoid smoking
- Screening (U/S ± CA125, Genetic testing)?
- Prophylactic oophorectomy

# Characteristics Relevant to Ovarian Cancer Screening

- Ovaries are inaccessible for direct evaluation or sampling.
- The lack of understandable natural history and definitive premalignant stage
- Low prevalence of ovarian cancer
- Screening test(s) must have an unusually high sensitivity and specificity to have a positive predictive value to justify intervention
- Treatment of positive tests is highly invasive, morbid and may involve castration

# Ovarian cancer

- Preoperative diagnosis
- Specialist referral
- Proper staging
- Debulking and cytoreduction
- Chemotherapy
- Palliative care

# Ovarian cancer 5 year survival by stage

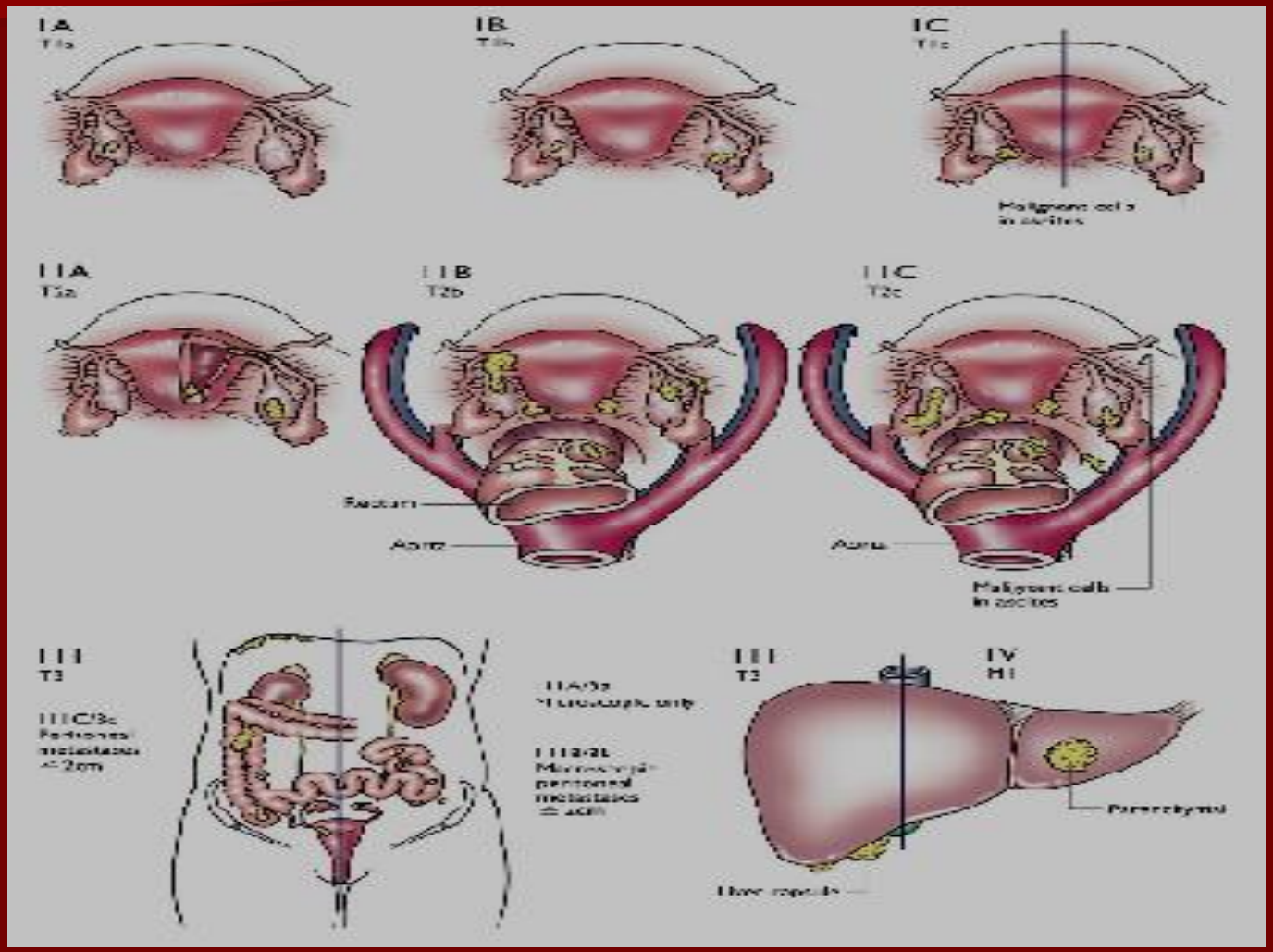
Table 11
Carcinoma of the ovary: patients treated in 1996–98. Epithelial ovarian cancer (obviously malignant cases). Five-year survival by stage

| Vol. | Year | Cases (*n*) | Ia | Ib | Ic | IIa | IIb | IIc | IIIa | IIIb | IIIc | IV | Overall % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | 1958–62 | 2320 | 60.7 | (Ib–IIa) 42.0 | | | 31.6 | | (IIIa–IIIc) 6.9 | | | 2.6 | 26.8 |
| 16 | 1963–68 | 4588 | 66.7 | 51.9 | | 49.7 | (IIb–IIc) 38.0 | | (IIIa–IIIc) 8.6 | | | 5.0 | 27.3 |
| 17 | 1969–72 | 4892 | 72.0 | 62.5 | 57.4 | 52.2 | (IIb–IIc) 37.5 | | (IIIa–IIIc) 10.8 | | | 4.6 | 30.1 |
| 18 | 1973–75 | 5268 | 69.7 | 63.9 | 50.3 | 51.8 | (IIb–IIc) 42.2 | | (IIIa–IIIc) 13.3 | | | 4.1 | 30.5 |
| 19 | 1976–78 | 6724 | 72.3 | 56.1 | 58.1 | 47.7 | (IIb–IIc) 42.1 | | (IIIa–IIIc) 13.5 | | | 4.5 | 29.8 |
| 20 | 1979–81 | 8082 | 76.6 | 67.7 | 59.6 | 51.1 | (IIb–IIc) 43.5 | | (IIIa–IIIc) 17.4 | | | 4.7 | 30.9 |
| 21 | 1982–86 | 10912 | 82.3 | 74.9 | 67.7 | 60.6 | (IIb–IIc) 53.8 | | (IIIa–IIIc) 22.7 | | | 8.0 | 35.0 |
| 22 | 1987–89 | 2942 | 83.5 | 79.3 | 73.1 | 64.6 | (IIb–IIc) 58.0 | | (IIIa–IIIc) 22.9 | | | 14.3 | 39.1 |
| 23 | 1990–92 | 7059 | 83.5 | 71.3 | 79.2 | 66.6 | 55.1 | 57.0 | 41.1 | 24.9 | 23.4 | 11.1 | 41.6 |
| 24 | 1993–95 | 3409 | 89.9 | 84.7 | 80.0 | 69.9 | 63.7 | 66.5 | 58.5 | 39.9 | 28.7 | 16.8 | 48.4 |
| **25** | **1996–98** | **4116** | **89.3** | **64.8** | **78.2** | **79.2** | **64.3** | **68.2** | **49.2** | **40.8** | **28.9** | **13.4** | **46.4** |
| **Total** | | **60312** | | | | | | | | | | | |

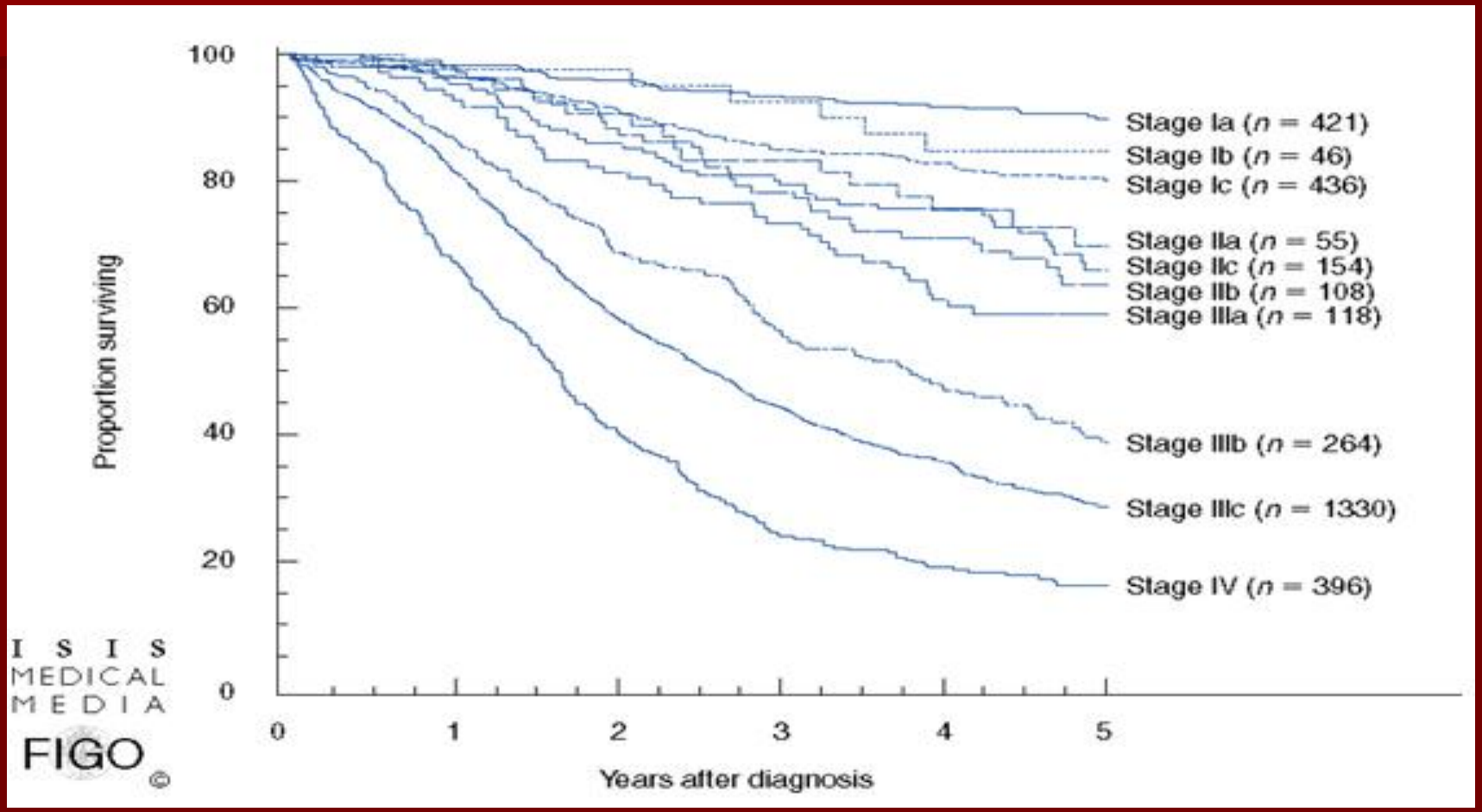
# Ovarian cancer: Preoperative diagnosis

- **Markers: CA125 ± (CEA, CA 19.9, hCG, AFP)**
- **Imaging: U/S, CT**
- **Risk of malignancy index: U x M x C**
  - **Benign ovarian mass**
  - **Suspicious or frankly malignant ovarian mass**

# Staging for Ovarian Cancer



# Ovarian cancer 5 year survival by stage



# Ovarian cancer specialist referral

- There is no place for casual surgery
- Preoperative anticipation is the core for optimum management
- Better outcomes in cases managed primarily
  by gynecologists than general surgeons
  by gynecological oncologists than generalists

*Nguyen et al. 1993, Kehoe et al.1994, Junor et al. 1999, Trope et al. 2006*

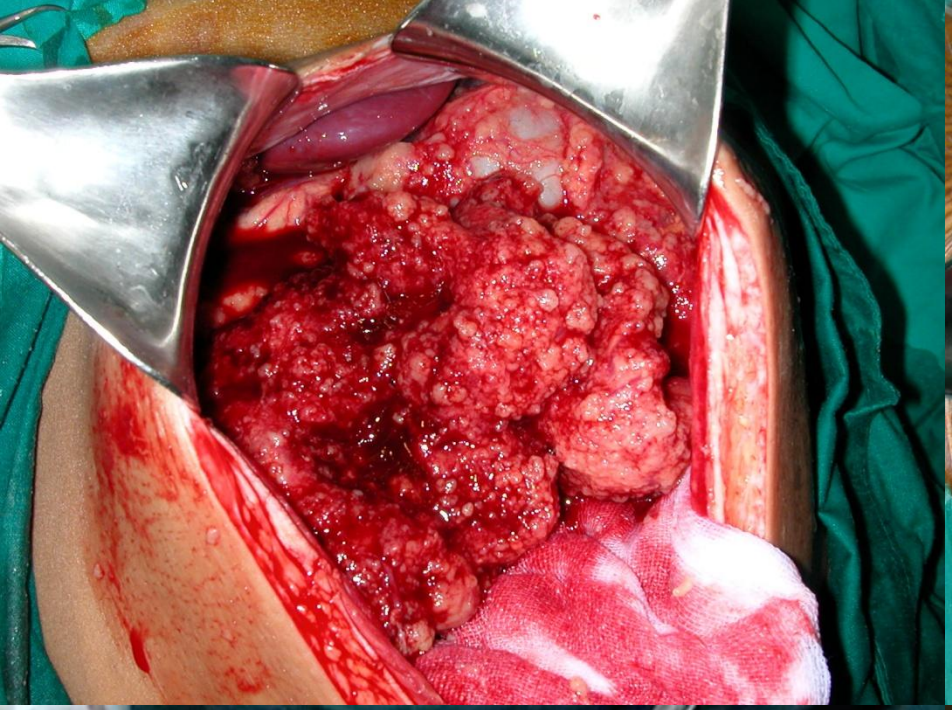
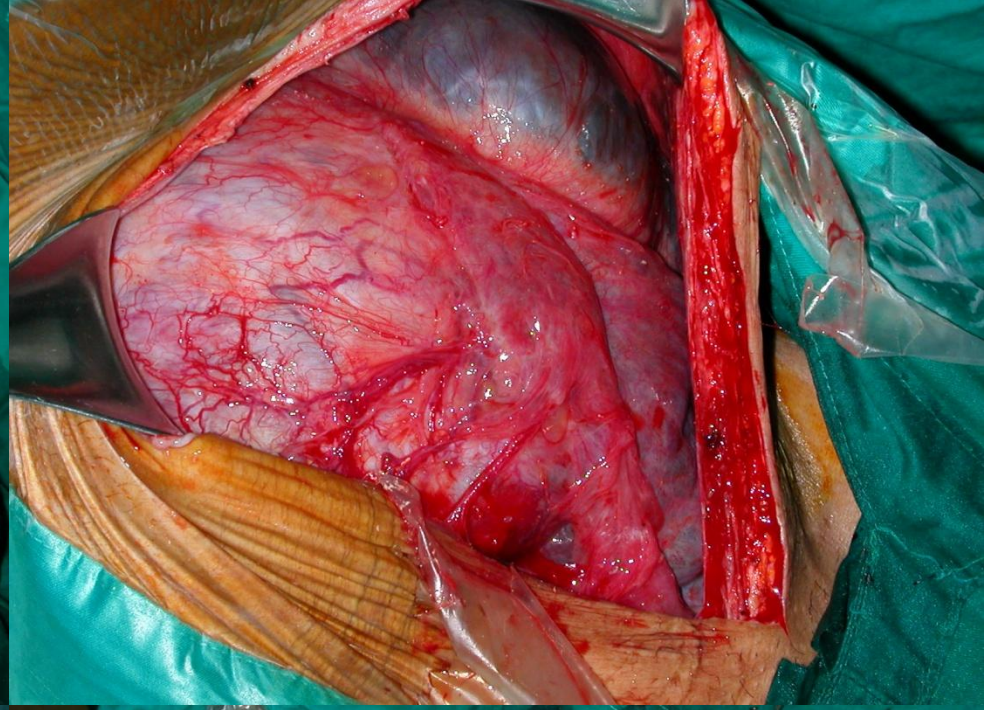
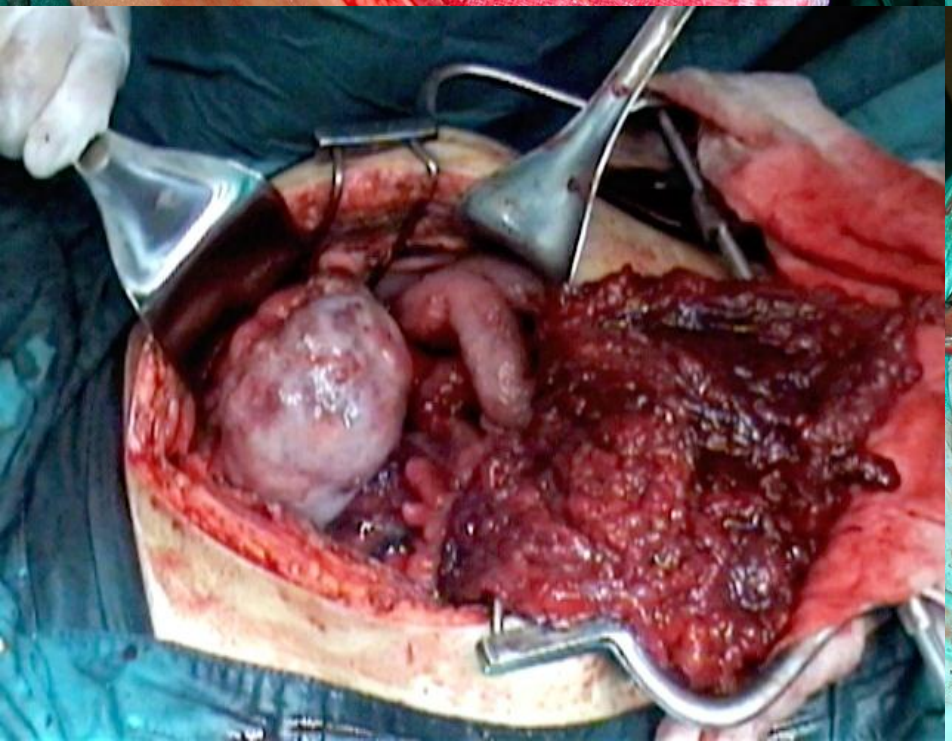
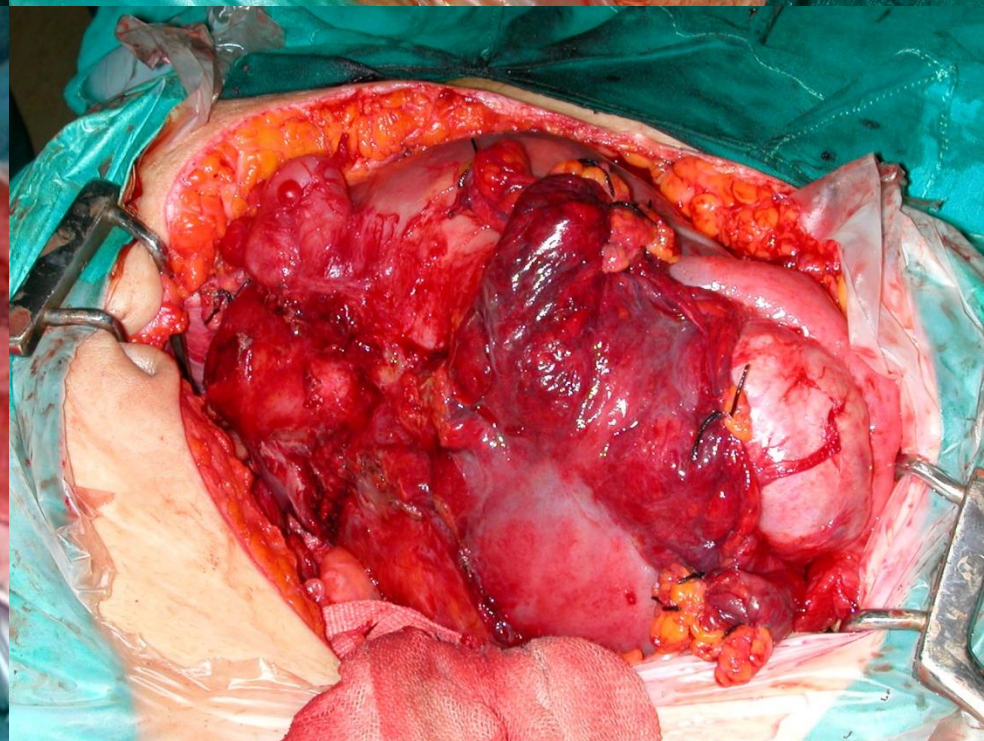

CLEMENTS

# Ovarian Cancer Staging

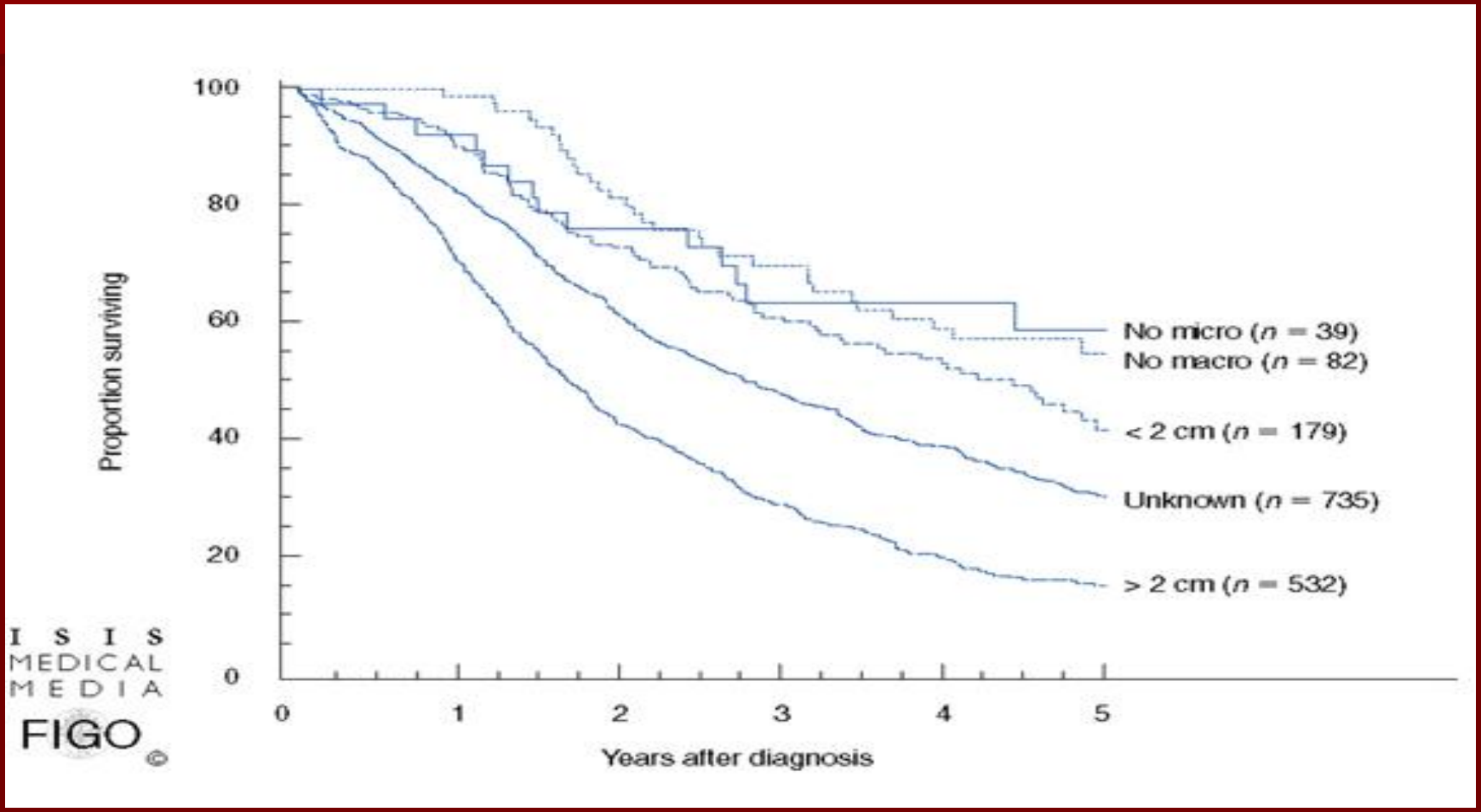
Proper staging is the corner stone of management

European guidelines of staging ovarian cancer EGSOC:

1. Peritoneal washing
2. Careful inspection & palpation of all peritoneal surfaces
3. Biopsy of any lesion suspect for metastases
4. TAH+BSO
5. Infracolic omentectomy
6. Biopsy or excision of any adhesion adjacent to the tumor
7. Blind biopsy of bladder peritoneum & POD (>=2)
8. Blind biopsies of paracolic gutters rt. & lt. (>=3)
9. Bind biopsy or smear of the rt. hemidiaphragm (>=2)
10. Blind biopsies of pelvic side wall at tumor side (>=2)
11. L.N.sampling along ext. & common iliac a. & v.
12. L.N. sampling along aorta & IVC up to lt. renal v.

# Survival by completeness of surgery



# Ovarian cancer debulking

Optimum maximum primary debulking

*leading to*

minimal residual disease

*followed by*

adjuvant chemotherapy

*used to be the*

gold standard

# Ovarian Cancer Chemotherapy

- Adjuvant
- Neo-adjuvant
- Consolidation
- Salvage

# Ovarian cancer chemotherapy

Taxol + Carboplatin

(GOG 158, AGO trial, Danish/Dutch trial)

is becoming the standard

*ICON3 & GOG 132 don't support that*

# Ovarian cancer chemotherapy
## Early stage adjuvant therapy yes/no ?

| | NO Pts. | OS | DFS |
|---|---|---|---|
| ICONI | 477 | 79 Vs.70% | |
| ACTION | 448 | 85 Vs 78% | |
| ICON 1 + ACTION | 925 | 82 Vs 72% | 75 Vs. 65% |

# Ovarian cancer chemotherapy
## Early stage adjuvant therapy yes/no ?

- Chemotherapy improves survival and disease free survival, hence everybody has to receive chemotherapy;

- Staging is a prognostic factor and the better the staging, the better the prognosis, hence everybody has to have optimal staging.

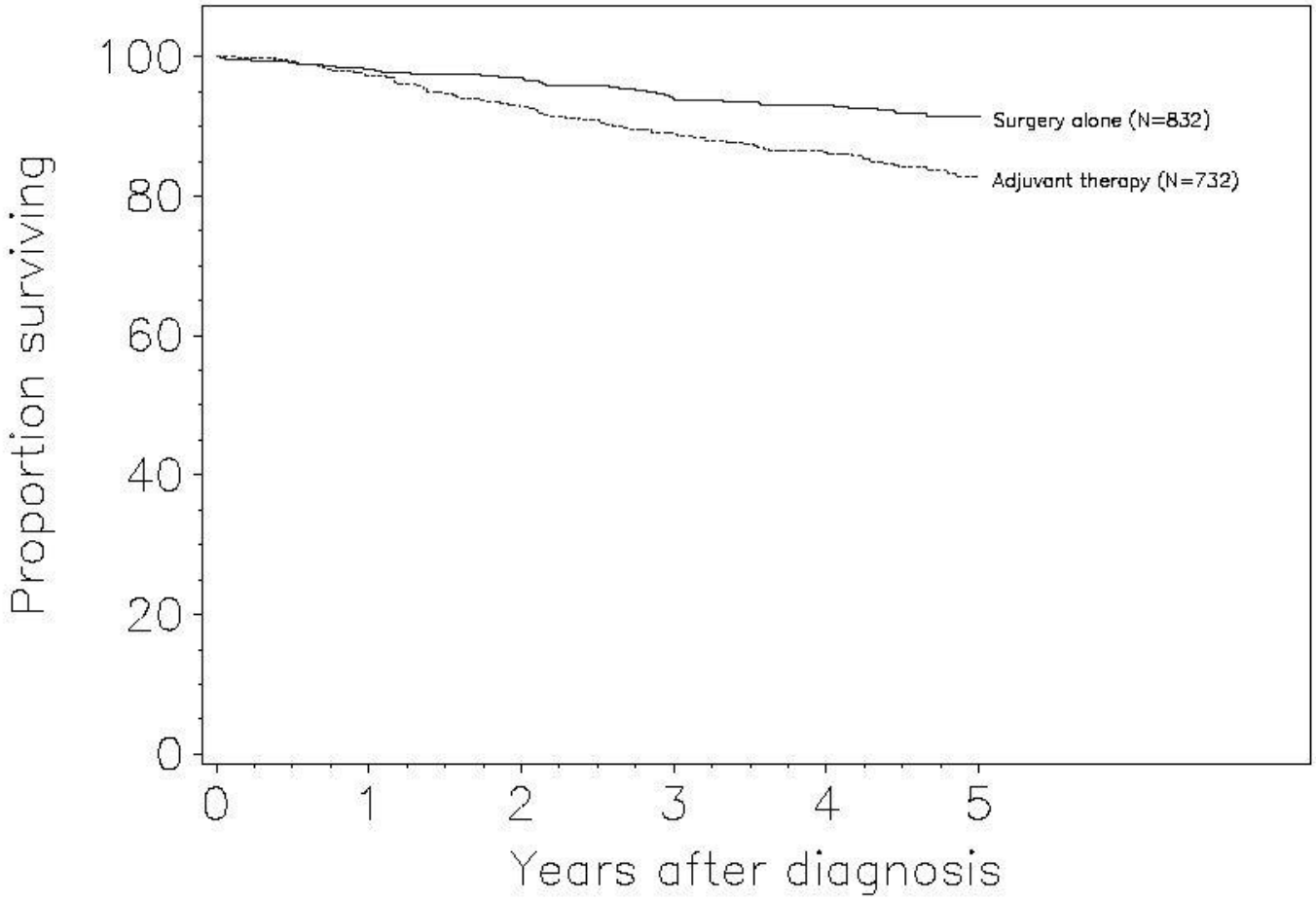
# Ovarian cancer chemotherapy
## Early stage adjuvant therapy yes/no ?

- Chemotherapy may correct for poor staging, hence all poorly staged patients have to get chemotherapy;

- Chemotherapy does not work in optimally staged patients, hence omit chemotherapy in patients that had optimal surgery.

# Adjuvant therapy for stage I

## *FIGO Report 2003*



# Late stage III/IV upfront chemotherapy followed by interval debulking ?

EORTC trial & MRC OV 06 trial

Vs GOG secondary debulking

# Primary chemotherapy for advanced disease

- Interval debulking surgery after platinum based chemotherapy is effective in prolonging overall and progression free survival in patients who would not be optimally cytoreduced by primary surgery

- The suitability for either optimum primary or interval debulking needs specialist evaluation and histological confirmation of the ovarian pathology (Radiological, biochemical markers, cytologic)

# Prior neoadjuvant chemotherapy has the advantage of:

- Improves patient's performance status
- Reduces tumour volume to be debulked
- Reduces ascites and pleural effusion
- Increases the rate of optimal cytoreduction
- Reduce operative morbidity
- Defines a group of patient with more favorable tumour biology and prognosis

# Adjuvant intraperitoneal chemotherapy

Vs

Intravenous chemotherapy

# Adjuvant intraperitoneal chemotherapy

- For optimally debulked advanced ovarian cancer (III)
- Better overall and disease free survival

*Alberts et al. 1996, Markman et al. 2001, Armstrong et al. 2006*

- Only 42% of patients received six cycles of designated intraperitoneal therapy
- 34% of patients received only one or two cycles
- Intraperitoneal catheter related complications reach 40% *Walker et al. 2005*

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COMMENTS AND CONTROVERSIES

# Intraperitoneal Chemotherapy in Ovarian Cancer Remains Experimental

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Andreas du Bois, *Department of Gynecology and Gynecologic Oncology, Dr Horst-Schmidt-Klinik, Wiesbaden, Germany*
Ignace Vergote, *Division of Gynecologic Oncology, University Hospitals, Katholieke Universiteit Leuven, Leuven, Belgium*

Intraperitoneal (IP) chemotherapy was not standard treatment for patients with optimally debulked ovarian cancer before January 4, 2006. A National Cancer Institute (NCI; Bethesda, MD) statement posted on the Internet[1] proclaims a change of practice, and it followed the publication by Armstrong et al and an accompanying editorial in the *New England Journal of Medicine*.[2,3] The NCI press statement talks about "prejudice" against the old idea of IP chemotherapy but apparently there is "now firm data showing that we should use a combination of IP and intravenous (IV) chemotherapy in most women with advanced ovarian cancer who have had successful surgery to remove the bulk of their tumor." The Chairman of the Gynecologic Oncology Group (GOG) states in the same NCI announcement that randomized multicenter trials, including that of Armstrong et al "clearly show the value of IP chemotherapy."[1] The President of the Society of Gynecologic Oncology says that she now knows that "the longest survival may be achieved by giving chemotherapy directly into the abdomen."[1] Finally, the Chairman of the Board of the Gynaecologic Cancer Foundation is quoted as looking forward to working with the NCI and the ovarian cancer community "to educate women about the results of this very important clinical trial."[1] Well, let three European oncologists help in this education process.

Furthermore, more patients in the experimental arm (IP chemotherapy) were lost to follow-up, compared with those treated in the control arm (11 *v* five patients). Such differences are not usually a concern. However, there were 127 and 101 patient deaths in the control and IP arms of the trial, respectively, and as few as three additional patient deaths in the IP arm could make the result nonsignificant. The statistical difference between the two arms of the trial is so marginal that these differences in eligiblity or loss of follow-up need to be investigated further.

The absolute difference in patients alive (15 patients) was less than those patients lost to follow-up (16 patients; 11 in the IP arm) and this is a very small proportion of the total population. It must be questioned whether such toxic treatment should be introduced as standard, based on such small differences and patient numbers.

In addition, the difference with respect to progression-free survival (PFS) was even smaller (nine more patients alive without recurrence in the IP arm), and comparisons for PFS failed significance ($P = .05$). Taking into account that in the end all patients with relapsed ovarian cancer will die, the difference with respect to survival will decrease further over time, and possibly fairly quickly given the statistical marginality of the overall survival benefit.

The main difference between the two arms of the trial oc-

# Recurrent ovarian cancer

Prognosis is related to

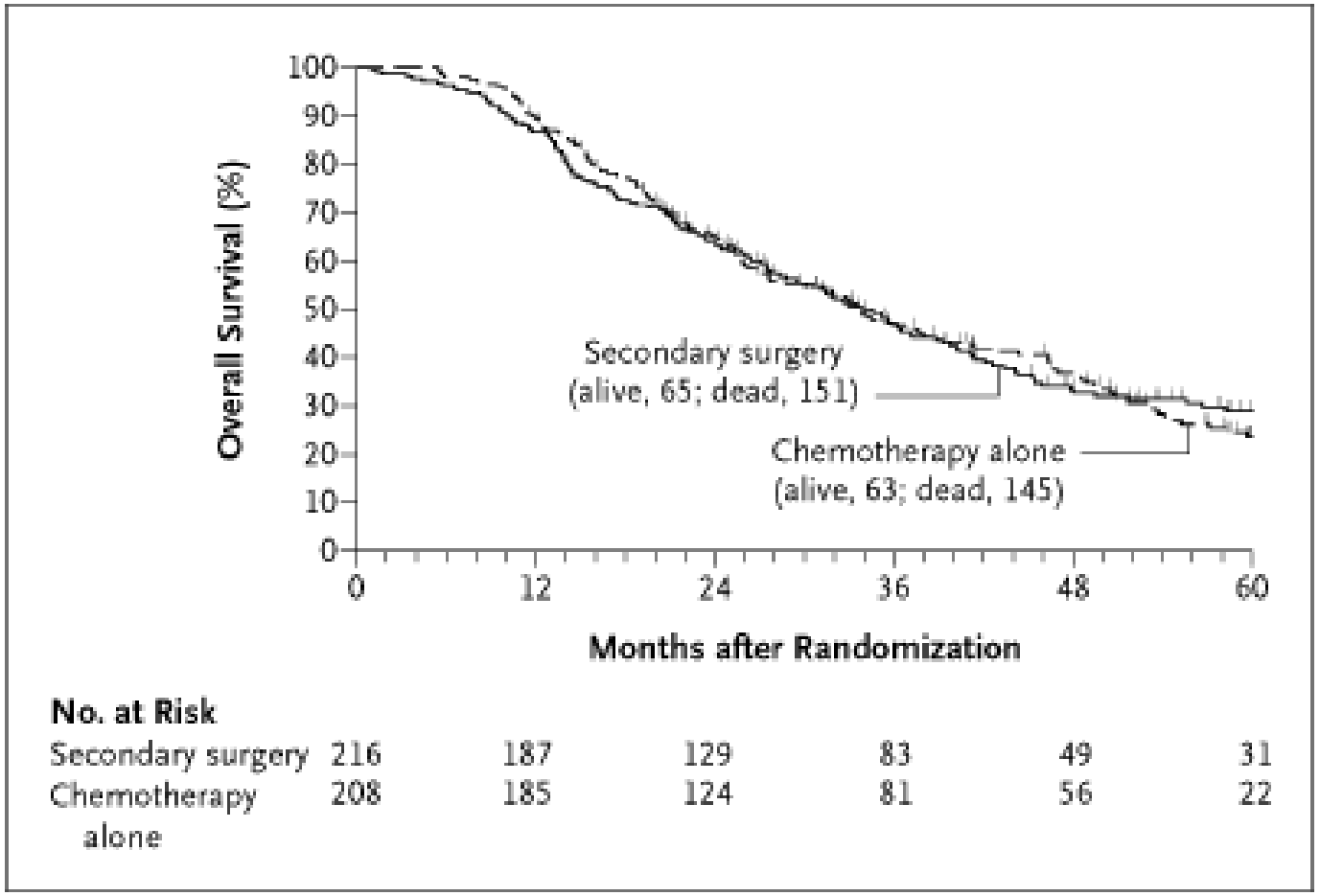
1. site of recurrence
2. duration since completion of therapy *(disease progression free interval)*
3. tumour's primary responsiveness to chemotherapy

# Recurrent ovarian cancer

Secondary debulking surgery is rarely done if :

- Localised recurrences
- Tumours that relapsed after more than 12 months *(survival benefit only if >2 years)*
- Value for secondary debulking if tumour can be reduced to no residual disease *(DESKTOP study 2004)*
- Tumours that were primarily responsive to chemotherapy

# GOG secondary debulking 2004



# GOG secondary debulking 2004